A GUIDE TO THE RECENT LITERATURE ON ASPERGILLOSIS AS CAUSED BY ASPERGILLUS FUMIGATUS

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A GUIDE TO THE RECENT LITERATURE ON ASPERGILLOSIS AS CAUSED BY ASPERGILLUS FUMIGATUS

By P. B. Marsh, P. D. Millner, and J. M. Kla[1/]

ABSTRACT

Spores of Aspergillus fumigatus Fres. have been found to be abundant in the atmosphere where large-scale experimental composting of sewage sludge is in progress at Beltsville, Md. The health implications of this finding for this and other sites are not completely understood. Studies are being made to characterize absolute concentrations of the fungus spores at this site, their dispersal by air from these composting operations, and their background environmental levels in air.

This report contains a list and review of references, many published since 1968, on the health effects of A. fumigatus. It is intended primarily to aid individuals interested in sludge composting and desiring an insight into the A. fumigatus-composting situation, but it may also interest those concerned with other substrates that become moldy at 40°-50° C.

The practical merits of sludge composting have been described elsewhere. The information here pertains mainly to the requirements for selecting composting sites and the process and design criteria at these sites.

KEYWORDS: Aspergillosis, Aspergillus fumigatus, compost, fungi, secondary infection, sludge.

INTRODUCTION

During an investigation at Beltsville, Md., into methods for composting sewage sludge, a question was raised concerning the possibility that the fungal pathogen Aspergillus fumigatus Fres. might present a health hazard at and around composting operations. A preliminary, semiquantitative examination of the air at a composting site had revealed that the organism occurred there at levels far above those at distant locations (92).2/ Wood chips used in the process appeared to be a major source. Thus, although sludge composting is basically useful (33, 104), the possible need for consideration of A. fumigatus-associated problems in site selection and details of the composting process has recently attracted much interest among individuals concerned with composting.

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2/ Underlined numbers in parentheses indicate the references at the end of this report.

The occurrence of A. fumigatus at the Beltsville composting site was not surprising, because the fungus is known to grow and sporulate profusely on damp hay, wood chips, and other self-heating organic matter (92, 114). The magnitude of any possible consequent health problem in connection with sludge composting, however, is still not completely known. Uncertainty on this subject derives in part from a lack of information. Data are needed on the numbers of A. fumigatus spores emitted into the air during composting, the extent of their aerial dispersal into adjacent areas, and the number already in the environmental background. Air samplings for these data are in progress. Additional uncertainty may be related to an insufficient understanding on the part of compost scientists and responsible officials of the health implications of A. fumigatus, i.e., what adverse effects it can cause, to whom, and under what circumstances.

The authors of this report considered that a record of recent literature on the health effects of A. fumigatus might be helpful to individuals in evaluating plans for specific compost operations. The purpose of the report is to assemble references useful to interested persons in arriving at their own independent, informed judgments on this matter and to provide a brief informational background helpful in such an endeavor. In the information provided, medical judgments generally reflect those of the authors cited.

SOURCES OF INFORMATION

The exact number of published papers on the health effects of A. fumigatus on humans is not known but probably exceeds 500. Articles appear in a wide variety of journals. Attention is focused here mainly on those published since 1968.

An excellent overview on aspergillosis can be found in texts on medical mycology by Rippon (118) and Emmons et al. (31). Individuals needing a more detailed examination of one or more aspects of this disease can find in this report a means of selective entry into a voluminous and rapidly increasing body of additional published information, much of it relatively recent.

The literature on aspergillosis may be located in several ways. One convenient method, in addition to this report, is to refer to the "Review of Medical and Veterinary Mycology" (1), which has current abstracts in English from a wide range of sources in several original languages; relevant references are grouped under the heading "aspergillosis." Some papers cited here contain lengthy lists of additional references. Computer services for reference search may be helpful. Papers cited here were selected mainly for their recency and the availability of the article in its original published form but without reference to the author's viewpoint.

Only briefly mentioned here are the direct effects of inhaled spores of A. fumigatus acting as an extrinsic allergen in the lung, i.e., without major growth in the body. Such allergies, although fairly common and occasionally associated with serious health problems, are also caused by spores of many other fungi and actinomycetes (8). Spasmodic bronchial response to such spores, as well as to dust, chemical vapors, and many other allergens, is common among asthmatics. Among nonasthmatics, sensitization to fungal spores can occur with repeated exposure to high spore concentrations. The typical response includes

a temporary episode of difficulty in breathing, nausea, and fever, beginning 4 to 6 hours after exposure (52, 168). This phenomenon is described in the literature under the terms "farmer's lung" and "extrinsic allergic alveolitis." Fungal infections within the ear are not considered here, even though A. niger van Tieghem or A. fumigatus may be involved. For information on this subject, see Rippon (118) and Emmons et al. (31).

Information on factors influencing distance of movement of fungus spores in air is relevant in some situations in which buffer zones between composting sites and hospitals or other health-care facilities are contemplated. Information on fungus spores in air has been summarized by Gregory (47).

As general background, the authors recommend a review by Lowrance (82), which contains a penetrating analysis of health-risk assessment as it relates to evolving public policy. The present paper hopefully represents a useful contribution to the careful fact-finding process regarded by Lowrance as a prerequisite to risk assessment.

EARLY STUDY OF ASPERGILLUS FUMIGATUS AND ASPERGILLOSIS

A. fumigatus was well described in 1863 (114) and has been recognized for many years as a biological entity differing in morphology and behavior from other aspergilli. Much of the early literature about the fungus pertains to natural lung infections it causes in wild and domestic birds and also mycotic abortion in cattle and sheep (114, pp. 82-98). Study and publication on the animal-disease aspect of the subject are continuing (48, pp. 88-93), but, with a few specifically noted exceptions, all further reference here is to the disease in man, which was first reported in the mid-19th century (31, 118). It has been the subject of many accounts since then. The role of primary disease in predisposing man to attack by the fungus was known in 1900, whereas the role of cortisone and other drugs in reducing natural immunity to the disease has been recognized for about 30 years.

A. fumigatus has been observed repeatedly to occur in abundance in composts and other self-heating organic matter and in other natural situations where temperatures range from 40° to 50° C (7, 92, 114). It obviously has a competitive advantage over other organisms in natural situations at such temperatures. However, detailed information on its occurrence in nature, particularly quantitative information, is limited (114). The fungus can utilize inorganic nitrogen, requires no amino acids or vitamins for growth, and can use many sugars as well as cellulose (88) as a source of carbon. Under some conditions, it can form soluble byproducts toxic to animals, but the role of these toxins in disease production is not understood (62).

NATURE OF THE DISEASE

Numerous reports attest to the pathogenicity of A. fumigatus in individuals predisposed to it by certain prior health problems. It rarely, if ever, produces aspergillosis in those not already suffering from some other health difficulty, and thus it is termed an "opportunist."

Among the aspergilli, A. fumigatus is by far the most frequently reported species involved in growth and disease of the human body, although A. niger, A. flavus Link, and other species have also been mentioned (4, 5, 19, 171). Most citations here refer to disease attributed by their authors to A. fumigatus. Natural inoculation with A. fumigatus occurs usually, although not invariably, by inhaling the spores, which are 2 to 3 micrometers in diameter and thus able to enter the respiratory tract and penetrate readily to the alveoli (8). Growth may be confined to a noninvasive colonization of the air passages of the lungs and of preexisting cavities resulting from tuberculosis, sarcoidosis, or other causes. Occasionally, however, the fungus invades lung tissue. Infrequently it becomes disseminated from the lungs through the blood stream to the heart, kidneys, or central nervous system. Invasion and dissemination are invariably serious (5, 45, 72).

The colonization of cavities is often chronic and may be accompanied by the formation of "fungus balls," a cough bringing up mucus and blood, or both (67). The severity of such a disease can vary from mild to life threatening. A. fumigatus is the organism usually found in fungus balls, but other fungi have been reported (161).

Allergic bronchopulmonary aspergillosis as defined by Rippon (118) involves colonization of air passages and frequently has been preceded by asthma (10, 51, 57, 67, 74, 80, 99, 125, 139, 157). Several years often intervene between the onset of asthma and the appearance of aspergillosis (48, p. 112). Asthma without A. fumigatus colonization, however, has been reported to be common in the vicinity of Baltimore, Md., where sputum from only 2 of 54 asthma patients produced A. fumigatus on more than 1 occasion (3). All 54 patients in the study had shown significant reactions to one or more common antigens. Thirty-five were given additional skin tests with 1 or more Aspergillus antigens. Of these, 17 were considered positive, but the results were not judged to warrant a diagnosis of allergic bronchopulmonary aspergillosis. The authors (3) stated: "The association of bronchial aspergillosis and asthma may be more frequent in England, as most recognized cases have come from that country. The infrequency of aspergillosis in our series of asthmatic patients suggests that it is a rare cause of asthma in our area." Pepys (48, p. 111) stated, "Allergic bronchopulmonary aspergillosis is the major cause of pulmonary eosinophilia with asthma in the UK." Some uncertainty about constancy in the etiology of "bronchopulmonary aspergillosis" as defined by Pepys seems evident. He (152) stated in respect to Candida albicans (Robin) Berkh., "The possible participation of this fungus in patients with allergic bronchopulmonary aspergillosis has yet to be assessed, but I think that this is probable." Colleagues appear to question whether any Aspergillus is necessarily involved in every case considered by Pepys to exhibit allergic bronchopulmonary aspergillosis (152).

Contrary to the definition by Rippon (118, p. 409), some authors apply the term "allergic bronchopulmonary aspergillosis" to cases in which, in spite of other positive indications, no cultural proof has been provided of growth of any Aspergillus in the lungs (57, 74, 124). Others stress the importance of positive sputum cultures. For example, Khan et al. (70) reported that over 80 percent of the individuals considered in their study to have allergic bronchopulmonary aspergillosis exhibited A. fumigatus repeatedly

in sputum cultures. Llamas et al. (80) reported a case in which the fungus was clearly detectable in the bronchi by fiber optic methods and in bronchial washings.

Individuals of all races and both sexes are included among the reported cases of aspergillosis. Children and teenagers may be affected (19, 23, 57, 139, 155), but incidence appears to be greatest among older people (49), who are most likely to suffer from predisposing conditions.

OPPORTUNISM BY ASPERGILLUS FUMIGATUS

A. fumigatus has long been known as an opportunist that follows other health problems, especially, but not only, diseases and disorders of the lungs. Physicians reporting lung infections by this organism have recorded tuberculosis, sarcoidosis, histoplasmosis, chronic bronchitis, asthma, and emphysema as conditions believed or suspected to have been predisposing to aspergillosis in their patients. They have also mentioned cancer and leukemia as predisposing (37, 56, 108, 132). Aisner et al. (4), for example, stated: "Infection is the major cause of mortality in patients with acute leukemia and lymphoma....Fungal infections caused by Aspergillus spp. are second in frequency only to candidiasis in these patient populations. When present, Aspergillus infections are the major contributory factor to their demise." Bacterial and viral organisms of many kinds are also well known to represent a more serious hazard to compromised (i.e., immunity-impaired) than to noncompromised hosts (35). Diabetes has likewise been considered as predisposing in some cases (31).

Infection from any of a wide variety of opportunists (35), including A. fumigatus (6, 23, 46), is typical of the chronic granulomatous disease of childhood, a problem associated with an inherited immunity defect. A case involving A. fumigatus infection in the lungs and in skin lesions of a 3-year-old girl without apparent prior debilitating condition was reported in 1969 (155), seemingly a case of primary aspergillosis. More recent evidence regarding the same patient, however, has disclosed that chronic granulomatous disease was present as an underlying disease.3/

Underlying disease, however, is not the only factor favoring the development of aspergillosis. Treatment for disease may also predispose. Based on numerous case records since the 1950's, many physicians believe that aspergillosis and other opportunistic infections have increased in the population as a result of the use of antibiotics, immunosuppressants, cytotoxic drugs, and corticosteroids (e.g., cortisone, predisone) (31, 118). The effect has been demonstrated experimentally in mice. Treatment of mice with cortisone prior to inhalation of A. fumigatus spores increased mortality to 25-100 percent as compared with 0 percent for noncortisone-treated controls (162). Sidransky (135) performed and reviewed many experiments in which he and others have, by administering immunity-impairing drugs or conditions, stimulated pulmonary and disseminated aspergillosis in mice subsequently allowed to inhale spores of A. flavus. Rabbits treated with doses of cyclophosphamide equivalent to those used in leukemia or with therapeutic doses of methyl prednisolone exhibited greatly increased infection and mortality with a standardized dose of A. fumigatus spores (119).

3/ Personal communication, H. J. Nickerson, M.D., Marshfield, Wis., Nov. 1978.

Although apparently not clearly proven, inhalation of massive doses of A. fumigatus spores might possibly overwhelm the immunity system and cause infection in a previously healthy individual (118). In any event, no data on dose-response relationships seem to be available in the literature for either predisposed or nonpredisposed persons. Austwick (7, 8) indicated that incitement of respiratory allergy probably requires a very low minimum level of inhaled spores, with higher levels needed to produce chronic infection, and still higher ones for acute infection. Differences in host resistance are obviously also of major importance. He stated (in 114, pp. 109-110), "Many factors enter into the establishment of infection in man and animals by aspergilli, but the number of conidia taken into the body is the main external one."

In some cases, invasive aspergillosis represents an end-stage complication in a person already seriously ill from an underlying disease and susceptible to attack by any of several commonly present opportunists (91). In other cases, it is a major contributor to an overall health problem. It may severely affect a person who is coping moderately or even very well with an underlying disease or health difficulty. Blank and Castellino (13), for example, stated: "The problem of pulmonary infection in patients with altered immunity is formidable. If infection in these patients only occurred concomitant with end-stage disease, there would be less sense of urgency in its management. In fact, however, infection often supervenes when the patient has achieved a modus vivendi with his underlying disease, or in the case of a transplant recipient, when he has successfully emerged from a rejection episode, or even when rejection has not been an immediate threat. Therefore, the prompt recognition of infectious complications, identification of the organisms responsible, and institution of appropriate treatment are critical."

CLINICAL OBSERVATIONS

Many authors assert the great difficulty of diagnosing aspergillosis (5, 65, 95, 96, 117, 151, 152, 163, 164) and also the inadequacy of known therapeutic measures (153, 164). Details may be found in papers on allergic bronchopulmonary aspergillosis (2, 17, 21, 29, 43, 51, 57, 59, 67, 70, 71, 74, 77, 87, 99, 100, 103, 109, 112, 128, 129, 133, 152, 157, 159), aspergilloma (12, 24, 31, 53, 86, 100, 115, 118, 131), problems with growth around prosthetic heart valves and elsewhere in the circulatory system (20, 40, 65, 111, 121, 148), myocardial infections (163), infections in the central nervous system (45, 60, 68, 72, 94, 95, 102, 134, 156), and on the related subject of extrinsic allergic alveolitis (8, 48, 66, 97, 159, 168).

Aspergilloma, involving fungus balls growing in preformed cavities resulting from tuberculosis, sarcoidosis, or other causes, is characterized by repeated episodes of coughing up blood, ranging from small amounts to a fatal hemorrhage (118, p. 411). In another noninvasive situation, the fungus may grow and stimulate mucus production in the bronchi. Related histology has been described in detail by Katzenstein et al. (67).

As many of these papers indicate, the prognosis for patients with the invasive and disseminated forms of aspergillosis is poor and few survive. The organism usually spreads through the bloodstream and often grows luxuriantly in

blood vessels. In disseminated disease, post mortem examinations have often revealed A. fumigatus as the cause of death when cultures from the patient's blood and other ante mortem diagnostic methods have failed to indicate its presence (65, 111, 127, 163). "Vegetations" of A. fumigatus, i.e., hyphal masses of the fungus, growing around prosthetic heart valves may cause their failure to function, and plugging of vessels by the fungus may also occur (65, 111). The authors cited here recorded that infections in the brain and spinal cord are usually fatal. Numerous accounts pertain to serious and often fatal infections in immunosuppressed kidney transplant recipients (16, 60, 76, 96, 117) and in individuals already affected with leukemia (37, 120, 132, 133, 164) or cancer (4, 5, 13, 37, 56, 91, 120, 151, 153). Pleural infection by A. fumigatus has been reported, but infrequently. It is sometimes fatal (90).

Growth of A. fumigatus may occur in the paranasal sinuses. In recent reports of individual cases (86, 147), surgical removal of the hyphal mass is described, and references relating to further cases are included. A case involving the paranasal sinuses and periorbital tissues with extension to the bone and repeated recovery of A. fumigatus is described by Emmons et al. (31, p. 294).

Entry of the fungus into the body during surgery and testing in hospitals, particularly in heart surgery (65, 111), represents an increased risk. In one case, the patient died following peritoneal dialysis and a resulting major infection by A. fumigatus (127). Rippon (118, p. 417) especially mentioned hospital-acquired or "iatrogenic" aspergillosis and noted a personally observed case following disk fusion.

A case of massive Aspergillus growth in the kidney following obstruction in the flow of urine has been reported (28). None of the predisposing factors so commonly found to precede such infection were present, e.g., malignant disease, insulin-dependent diabetes, or corticosteroid therapy.

Surgical removal of A. fumigatus-colonized lung tissue has been practiced for many years, apparently with a moderate frequency of success (73, 115, 118). Varkey and Rose (154), however, stated, "Contrary to the conclusions of previous reports, the experience in our series of patients suggests that routine surgical excision of aspergilloma is not indicated." Reservations about the efficacy of such routine surgical removal also have been expressed by some authors (48, pp. 148-151). Still others (145) concluded that "excision of a solitary 'fungus ball' is recommended."

No regularly effective antimicrobial treatment against A. fumigatus infection has been reported (153). Amphotericin B has been tried many times but with only occasional success (50, 103, 115, 153, 165). Aisner et al. (5) found that early and aggressive diagnosis followed by prompt use of amphotericin improved chances of survival in cancer patients, but the drug has a high potential for causing kidney damage. Rippon (118, pp. 534-538) provided a general summary of experience with amphotericin in the control of several fungus diseases.

Some of the numerous reports on serological phenomena and test procedures in relation to A. fumigatus are cited here (9, 24, 25, 44, 75, 76, 87, 89, 106,

107, 109, 125, 126, 130, 132, 141, 150, 158, 167). Basic knowledge and techniques in this field are changing so rapidly that even relatively recent conclusions may quickly become outdated. As indicated in the following papers, many authorities currently place only limited reliance on serological results as an independent criterion in diagnosing aspergillosis.

Patients with widespread invasive aspergillosis, which was mostly confirmed later at autopsy by cultures of A. fumigatus, showed no detectable antibodies to the fungus in their serum (169). According to Emmons et al. (31), "Immune mechanism of these patients has been altered by severe underlying diseases and/or immunosuppressive therapy." Patients with noninvasive forms of the disease are more likely to exhibit positive results in precipitin tests and to Aspergillus antigen in skin tests (31, p. 298). Rippon (118, p. 424) stated: "Precipitins are always present in aspergilloma patients. This is especially useful for diagnosis when sputum is culturally negative due to lack of connection of the cavity with a patent bronchiole."

Regarding asthmatics, Emmons et al. remarked (31, p. 66): "Precipitin antibody can be demonstrated in approximately two-thirds of asthmatic patients with pulmonary infiltrations. The relationship of these antibodies to whatever fungal infection is or had been present is not clear, however." Tosh (150) wrote: "The lack of specificity of serological tests is not limited to the fungal diseases, but it may be more common in fungal serology because many of the fungi appear to share common antigens. Experienced investigators in the field accept cross-reactions as a fact of life and rely upon other diagnostic procedures to establish the correct diagnosis."

Bardana (9) concluded that "nearly everyone has some circulating antibody to aspergilli" and that "with the possible exception of untreated aspergillomas, immunological testing cannot be exclusively relied upon to discriminate aspergillus-induced syndromes consistently." He also noted that "commercial preparations of house dust contain antigens which share antigenicity with A. fumigatus." Jameson (63) reported antibodies to certain components of some extracts of A. fumigatus in a high proportion of normal serum, and Reed (116) similarly stated that "approximately 2% of the group of healthy Madison dwellers had precipitins to A. fumigatus." Malo et al.(87) remarked that the presence of precipitins against A. fumigatus has been reported in asthmatics without evidence of aspergillosis, and that "the results of precipitin tests have to be interpreted in the light of clinical findings."

Katzenstein et al. (67) warned that "the significance of serum precipitins to Aspergillus must be interpreted with some caution." Referring to allergic bronchopulmonary aspergillosis, they stated, "Similarly, skin tests with Aspergillus antigens, while usually required for diagnosis, also are not highly specific for this condition." Gordon et al. (44) claimed high specificity for a modified indirect fluorescent antibody test that uses germinated spores or "germlings" of A. fumigatus rather than hyphae. More experience with this recent test seems desirable.

Rippon and Anderson (119) stated that "personal experience and that of others...indicate that these tests (immunodiffusion, complement fixation and indirect fluorescent antibody) are usually lacking in definition in sera from patients with systemic invasive aspergillosis."

Louridas (81) found that intradermal testing with A. fumigatus produced only a low degree of specificity. A much higher proportion of asthmatic than nonasthmatic subjects yielded positive skin test results. In a group of 534 asthmatics, 130 exhibited positive skin test results, but of these 130, there were 109 who responded to other antigens also. The author (81) stated that "109 of the patients who exhibited multiple cutaneous allergies were probably atopic subjects in whom the specific significance of a positive Aspergillus skin test is doubtful." Eleven positive skin test results were observed in supposedly healthy control subjects showing no other sign of disease. The author contended, "The absence of other positive tests supports the innocuousness of skin reactivity." In agreement with these findings, Reed (116) stated: "Another problem with the skin test as a diagnostic procedure is that it is not specific for allergic aspergillosis. For example, in a group of asthmatic patients without aspergillosis and a group of 'normal' subjects, skin test results were positive in 12% and 4%, respectively."

The work of Chen and Chuang (22) demonstrated clearly the high frequency of positive dermal and inhalation challenge responses to many fungi among asthmatics. The results of 2,960 intradermal tests and as many scratch tests on 488 asthmatic patients and 112 healthy persons with antigenic extracts of 10 fungi showed that positive reactions were much more common in asthmatics than in healthy persons. Of 618 bronchial sensitivity tests with fungus extracts on asthmatics, 50 percent showed positive responses. Bronchial tests were positive in the majority of patients who had positive skin tests to the same antigens and negative in most patients with negative skin tests. Many of the asthmatics responded to house dust as well as to spores.

A rising level of total serum immunoglobulin E (IgE) was reported among a group of 12 patients with allergic bronchopulmonary aspergillosis (ABPA) during periods of flare in disease activity manifested by new roentgenographic infiltration or more than 3 days of fever, chest pain, and cough with purulent sputum or hemoptysis (58). A stable or declining IgE level was associated with disease remission. No clear relationship of the changes in IgE level to activity of the fungus was shown, nor is it evident that the proven presence of any Aspergillus in the patient was required for the diagnosis of ABPA in this study (58). Precipitins and IgE antibodies to A. fumigatus and other aspergilli occurred much more frequently in individuals with cystic fibrosis than in control subjects (41, 89).

Comments on the interpretation of radiographs in regard to growth of A. fumigatus in the bronchi have been provided by Simon (136, pp. 69-74). He stated, "A bronchogram is rarely needed for diagnosis, but if one is done, evidence of bronchial damage is usually obvious." Accordingly, three patients with clinically evident allergic bronchopulmonary aspergillosis had normal chest X-rays but showed evidence of bronchiectasis in bronchograms (124).

Lung scans with radiostrontium have been suggested for diagnosis. Scans were positive for all 12 individuals already known to have allergic pulmonary aspergillosis or aspergilloma, negative for 13 control subjects, but positive for 4 other controls (2). A negative scan appears to exclude the diagnosis of

allergic pulmonary aspergillosis or aspergilloma, whereas a positive scan may be much less specifically informative.

Surgery may be used to establish diagnosis. McElvein (85) stated: "A patient with pulmonary fungal disease may have nonspecific respiratory symptoms, and the X-rays of the chest may be nondiagnostic. Skin tests and complement-fixation tests, because of cross-reactions and low specific antigenicity, are not always sufficiently precise to enable diagnosis with certainty. The surgeon can obtain material which should be handled properly and submitted to a good laboratory to establish diagnosis and to institute proper therapy."

The characteristic microscopic appearance of aspergilli in pathologic material was illustrated by Emmons et al. (31), who also described suitable culture methods and microscopic criteria for species identification in culture. The fungal hyphae display septation and typical bifurcate branching in tissue specimens and are easily distinguished from the wider, mostly nonseptate hyphae of Phycomycetes. Distinction between the hyphal forms of Petriellidium and Aspergillus in pathologic sections may be difficult or impossible unless the conidiophores of Aspergillus are present (83). The necessity of cultures in diagnosis is emphasized (48, p. 80), along with the comment: "So often the question of a fungal infection is first raised only after the only available specimen has been fixed in formalin or exposed to airborne contamination."

Emmons et al. (31) indicated that the spore-bearing apparatus in A. fumigatus is highly typical of the species. They stated: "The gradual widening of the tip of the conidiophore into a vesicle, production of phialides on only the upper half or two-thirds of the vesicle, production of primary phialides only, the bending of the lower phialides so that they approach a parallel orientation with those above, resulting in production of a columnar mass of conidia and the grey-green color of the colony are characteristics which easily identify this species." Photographs of the typical conidiophore structure in A. fumigatus have been published (31, 114, 118). Raper and Fennell (114) presented a comprehensive and detailed discussion of the morphology and taxonomy of the A. fumigatus group. Temperatures of 37° to 50° C tended to eliminate competing organisms in cultures with mixed inoculum and to facilitate detection of A. fumigatus (15). The use of oxgall in the medium decreased radial growth of colonies of fungi and thus limited confluence and facilitated counting (92).

Identification of the gray-green colonies of A. fumigatus in cultures from sputum samples has uncertain diagnostic significance unless the fungus is cultured rather consistently from a series of samples. Even then, the results might indicate only repeated exposure to inhalation of spores rather than internal growth (129). If positive cultures are obtained, then the presence of hyphal fragments, the typical conidiophores, or both in the original sputum increases the diagnostic value (32). Background information on the fungal flora of the sputum of healthy men has been provided by Comstock et al. (26). These authors offered the following interesting comment: "The role of fungi in bronchopulmonary disease is puzzling. Even when they are not dismissed out of hand as contaminants of the respiratory secretions, careful study may still fail to tell whether fungi caused the disease process as primary pathogens, aggravated it as secondary invaders, or as saprophytes merely found it to their liking." Isolation from sputum samples of aspergilli of many species present

as "transient residents in the human respiratory tract following their inhalation from the environment" has been reported by Sandhu and Sandhu (129). Sputum samples in some cases may contain mucus plugs with the fungus microscopically visible in them. In some patients they may also be visible in situ during the bronchoscopic examination (80).

EPIDEMIOLOGY

This subject is not well understood (137), probably largely because of inadequate reporting of cases. Obvious reasons for such reporting are the lack of reliable diagnostic techniques and the diverse aspects of the disease. Rippon (118, p. 408) remarked, "The pathogenic spectrum of aspergillosis is complicated, confusing,...and represents a group of diseases."

The bronchopulmonary phase of aspergillosis appears to have been reported more frequently from Britain than elsewhere (48, 57, 74, 109, 137), a situation that Solomon and Burge (143) tentatively attributed to "an atmospheric burden of A. fumigatus substantially lower, in our locality, than in Britain." Although the disease may actually occur more frequently in Britain, Parker et al. (103) stated, "Mainly because of the lack of diagnostic criteria and methods, there are no reliable data concerning the incidence of pulmonary aspergillosis in chest disease hospitals." Referring to the relatively low levels of allergic bronchopulmonary aspergillosis recorded for the United States compared with similar records for England, Pepys (110) commented: "Apparently, differences in recognition of the disease appeared to be related to the inadequacy of the antigens used for skin test diagnostic purposes. In a comparison of the incidence of allergy to Aspergillus fumigatus in centers in the United States and in London, the commercially supplied Aspergillus antigen mixture did not in fact contain the antigen being studied, namely Aspergillus fumigatus." Based on recent experience, Patterson (105) stated, "Allergic bronchopulmonary aspergillosis is not a rare disease in the United States despite the lag in recognition as compared with case discovery for many years in England." Without questioning the usefulness of intradermal and serological testing with Aspergillus preparations, some cases described as "allergic bronchopulmonary aspergillosis" do not involve a proven connection with any fungus. Two of three cases reported by Imbeau et al. (57), for example, seem to fall into this category. Critical proof of any particular fungus growing in the body seems also to be lacking in the studies of Rosenberg et al. (126) and Mintzer et al. (93). Cases of pulmonary aspergillosis in large numbers, often treated surgically, have been reported from Poland. For information on this, refer to numerous abstracts, not cited here, in the "Review of Medical and Veterinary Mycology" (1).

Records of incidence of hospitalized cases of systemic mycotic infections for the United States in 1970, including aspergillosis, have been collected by Hammerman et al. (49). The data show very low levels of aspergillosis, but the authors stated that they provided "undoubtedly a low estimate of the incidence of all infections discussed." Systemic mycoses were observed in 109 out of 5,142 autopsies, or 2 percent, at the University Hospital in Oklahoma City during 1955-75; 8 of the 109 cases were attributed to systemic aspergillosis (113).

In cane-sugar processing in India, 2 of 131 workers occupationally exposed repeatedly to high concentrations of A. fumigatus in air exhibited allergic bronchopulmonary aspergillosis as reported by Khan et al. (71). The authors concluded that "constitutional predisposition of the host may be a more important factor than the extent of exposure to the fungus in the development of allergic bronchopulmonary aspergillosis." Many other workers displayed chronic lung difficulties of uncertain etiology.

Although unusual among the fungi in its ability to grow within the human body, A. fumigatus is only one of many fungi and actinomycetes whose spores may act as extrinsic allergens in provoking asthmatic and other allergic responses within the respiratory system (8, 22, 118, pp. 502-507). The farmer's lung phenomenon occurring among mushroom compost workers and others (14, 77) is believed to result from a massive allergic assault on the alveoli by exceedingly large numbers of inhaled spores (77, 78). Unlike exclusively extrinsic allergens, which can often be avoided by restricting individuals from situations in which they occur, A. fumigatus can also grow internally in the air passages of the lungs and thus cannot be avoided by such simple means (107, 138).

RISK ASSESSMENT AND CONTROL

The obvious practical merits of sludge composting leave little doubt that one or several versions of the practice will be employed at some locations in the United States. The only questions are where will this occur and what composting processes will be used. Assessment of the health risk from point sources of A. fumigatus is complex and should include input from physicians familiar with aspergillosis working together with mycologists knowledgeable about A. fumigatus and others with relevant information. Professional personnel informed about aspergillosis can be located through medical schools or large hospitals or through authorship of the papers cited here.

Various verbal opinions have been expressed regarding the probable risk from A. fumigatus at and around sludge composting sites. Estimates of risk range from minor or nonexistent to significant and possibly major in some situations. The need to examine the facts, assumptions, and logic underlying such opinions is evident. Risk assessment is made difficult by (a) a shortage of data on background environmental levels for A. fumigatus in air, (b) lack of quantitative information on emission rates and spore dispersal patterns at composting sites, and (c) lack of a dosage response curve relating inoculum levels of the fungus to disease incidence in humans.

In respect to risk assessment in the situations under consideration, the authors find such statements as "we live in a moldy environment," "molds are all around us," and "aspergilli are ubiquitous" to be of questionable usefulness. "Ubiquitous" is nonquantitative, and A. fumigatus is frequently named as a species in individual medical reports rather than the less specific "Aspergillus sp." Although the literature cited here makes clear that aspergilli other than A. fumigatus can infect highly compromised individuals, the same literature makes equally clear that A. fumigatus is the most frequently recorded species among the aspergilli reported in the literature as a cause of infection in humans. Emmons et al. (31) stated: "Aspergillus fumigatus is the usual etiologic agent

of the pulmonary aspergillosis of the typical, severe, invasive form with eventual hematogenous dissemination to other organs....In its clinical manifestations, Aspergillus fumigatus is the most virulent and most versatile of the Aspergilli."

Many of the authors cited here appear to think of A. fumigatus as present at infective levels in all situations and to attribute overwhelming importance to the predisposed condition of the host compared to differences in inoculum level. For example, Rippon (118, p. 3) stated: "Opportunistic infections are caused by universally present organisms of low virulence. Establishment of disease depends entirely on lowered resistance of the host." Recent interest and action to control sources, situations, and procedures in hospitals that might lead to the presence of the fungus are reflected in numerous publications (4, 40, 60, 65, 76, 111, 120, 127, 148). Air sterility in operating rooms and intensive-care units in respect to A. fumigatus has been of particular concern. Kammer and Utz (65), for example, stated, "Careful surveillance and control of fungal contamination of the surgical environment is urged." Corrective actions to date have related mainly to hospital ventilation and air-filtration facilities (16, 40, 65, 111, 120, 122, 123). A few details recounted here may further reinforce for the benefit of planners and operators of composting ventures the fact that doctors are currently looking with increasing concern into the sources of inoculum of A. fumigatus in hospitals.

Gage et al. (40) reported Aspergillus endocarditis in three patients after heart surgery and ascribed the infection to growth of A. fumigatus on pigeon excreta near the intake of the ventilating system in the operating room. Burton et al. (16) isolated A. fumigatus from external air inlets to an isolation room after four cases of aspergillosis appeared in kidney transplant recipients. When the suspected source of infection was removed, no aspergillosis was observed in 20 subsequent kidney transplant recipients.

Petheram and Seal (111) reported seven cases of A. fumigatus prosthetic valve endocarditis and described the probable source of infection: "After identifying the first three patients in this outbreak, a careful search was made of the operating theatre environment for a possible source of entry of the spores. Green dust containing small natural and man-made fibres from theatre swabs and surgeons' gowns was collected from the ventilation system in quantities sufficient to fill a large sweet jar. Culture of this dust revealed a profuse growth of A. fumigatus." In another instance, hospital workers were unable to find an internal source of the fungus after four cases of aspergillosis appeared within a few weeks in an intensive-care unit (64). Staib et al. (146) suggested that airborne conidia exhaled by a hospital patient infected with A. fumigatus may serve as inoculum for another patient. They stated that their studies have "revealed that aspergillosis patients, clinical material sampled from them, decaying plant material (agriculture, horticulture), and used clothes and linen may form foci for the spread of A. fumigatus conidia."

Rose (120) reported: "Terminal Aspergillus pneumonia developed in 11 patients on the wards of an old, naturally ventilated hospital during the last five years of its occupancy. All patients were moved to a new, mechanically ventilated hospital and this infection was not seen during the next five years." Concerning their work, they wrote, "This study suggests that hospital-acquired

infections of the lung might be eliminated if all incoming hospital air is filtered, properly vented, and not recirculated." In a similar situation, Rosen and Sternberg (123) reported a decrease in the number of cases of aspergillosis and mucormycosis coincident with a move from an old into a new hospital. They tentatively attributed the improvement to "the elimination of some sources of contamination as a result of an improved ventilation system."

Aisner et al. (4) reported a cluster of eight Aspergillus infections in cancer patients within 7 months soon after their transfer to a new hospital facility. They developed strong circumstantial evidence that this striking increase in aspergillosis was traceable to fungal growth on fireproofing material used in the false ceiling of the new facility.

Solomon et al. (144) made fairly extensive volumetric air samplings for fungi able to grow at 37° C in a Michigan hospital and reported mean levels for A. fumigatus of less than 10 colony-forming units per cubic meter; the mean at an outdoor collection point was 6.3 per cubic meter. Their samples were 1.7-3.4 m^3 in volume. More than half of all indoor and outdoor samples contained the fungus in low but readily detectable amounts. They (144) contrasted their data with the generally higher in-hospital levels of A. fumigatus recorded by Noble and Clayton (98) and commented, "The possibility that A. fumigatus levels encountered by these workers were derived from discrete intramural sources is not easily dismissed."

The measured levels of A. fumigatus in air found by Solomon et al. (144) were of the same order of magnitude as reported earlier for outside air by Austwick (7) and Hudson (54). In summarizing his data Hudson (54) stated: "Some 550 colonies of thermophilous and thermotolerant fungi were isolated during the year. Total counts ranged from 0 to 14 spores/m^3 with a mean of 3.2 spores/m^3. This is extremely low, as might be expected when compared with the total counts of the mesophiles. At the same site, the mean concentration of mesophilous fungi in 1967 ranged from 330 to 12243 spores/m^3 (Hudson, 1969). Twelve fungi listed in Table 1, were encountered. Of these, Aspergillus fumigatus was by far the most common and made up 69.0% of the total count." Hudson's mean level for A. fumigatus was 2.21 spores per cubic meter. For comparison, total counts of all fungal spores in outdoor air in summer often exceed 10^4 per cubic meter (47), and counts of the same type in a barn containing moldy hay often exceed 10^7 per cubic meter (77). Further information on levels of A. fumigatus spores in air is provided by Burge et al. (15), whose aerometric spore counts per cubic meter for this organism taken inside 11 libraries at the University of Michigan averaged six in summer and zero in winter as compared with readings of zero and one outdoors in the same seasons.

When adequately investigated, the occurrence of A. fumigatus in nature may turn out to be governed largely by its ability, or lack of it, to grow at relatively low moisture levels. The very limited information now available does not suggest such adaptation to any high degree. In one report, growth of the fungus occurred on naturally infected hay at 42 percent moisture and was accompanied by heating to a maximum of 64° C, whereas at 28 percent moisture the growth consisted mainly of the low moisture-adapted A. glaucus group species and heating reached only 44° (7). In another report (48, p. 17), molding of hay was absent below 13 percent moisture, consisted of A. glaucus group species up to 25 percent

moisture, of A. versicolor (Vuill) Tiraboschi, A, nidulans (Eidam) Wint., and Absidia spp. at about 30 percent moisture, and was dominated by A. fumigatus, Mucor pusillus Lindt, Humicola lanuginosa (Griffon and Maublanc) Bunce, and certain actinomycetes above 40 percent. However, water potential may be more informative than water content.

In assessing any A. fumigatus-associated health risk that might exist at and around a composting site, one must consider the probable degree of predisposition of any individuals likely to be exposed and the number of such individuals. Proximity of the site to hospitals, nursing homes, medical clinics, doctors' office buildings, major blood-collection centers, and other health-care facilities may need to be examined closely. The possibility of serious consequences from A. fumigatus in a large hospital of diversified function has been emphasized in references cited in this report, and it seems reasonable to conclude that any activity resulting in heavy air contamination with the fungus in the vicinity of such hospitals should receive special attention. Not only open windows but also every individual entering the hospital from an outdoor parking lot may offer an avenue of entry for the fungus by mechanical transfer on hair, hands, and outer clothing.

Some nursing homes have individual window air conditioners in the patients' quarters. Their filters are generally much too coarse to prevent entry of spores of A. fumigatus. Although possibly presenting a less critical situation, composting sites near commercial establishments that manufacture and distribute surgical and medical supplies, vaccines, and pharmaceuticals may warrant precautionary consideration.

Safety-conscious operators of composting facilities might wish to use preemployment medical examinations to exclude predisposed individuals from their operations, possibly accompanied by postemployment monitoring. Both have been used with coal miners (69). Attention to any possible predisposing lung condition, especially asthma, would seem of concern. In a somewhat similar situation, Slavin and Winzenburger (140) recommended that doctors advise asthmatic patients who are organic gardeners against working with hot home compost piles because of the probable presence of high levels of A. fumigatus spores.

Clearly, the nature and magnitude of the composting operation itself may affect the level of spore emissions and must be considered in an evaluation. In plans for individual compost sites in the Washington, D.C., area, composting of as much as 600 wet tons of sludge per day has been envisioned.

The lack of quantitative data on the relationship of spore concentration of A. fumigatus in air to the occurrence of aspergillosis in man represents a major difficulty in risk assessment. In this predicament of logic, one may be forced to rely on "exposure relative to natural background" (82, p. 85). Thus, when naturally present levels of the fungus in the aerial environmental background become better known, some arbitrarily determined limit for imposed levels may be set relative to the background. Though not ideal, restrictions and regulations involving a similar logic have been imposed in many other health-risk situations (82).

Care in the assessment of risk should attend the use of the common terminology "secondary pathogen" as applied to A. fumigatus. As used with precision, this term signifies that the fungus is second in order of time sequence, following some prior adverse health development, and signifies nothing in regard to whether the effects of the fungus are of secondary importance or not to the health of the individual. Even greater care may be needed to avoid the loose application of the term "ubiquitous" to A. fumigatus. The word may be applied reasonably to the genus as a whole, but only on a much less factually verifiable basis to A. fumigatus.

Some persons tend to categorize aspergillosis as a "rare" disease, with concurrent implication that it may reasonably be predicted to remain so under all circumstances in the future, even with our changing patterns of life and environment. Apart from the uncertainty about current estimates of incidence, the logic of this argument seems to rest on the presumption that no increase in the disease would occur even if inoculum levels should increase greatly.

RISK ACCEPTABILITY

In a generalized presentation applicable to the entire problem of risk in the treatment and disposal of sewage wastes, Lowrance (82) noted that once a risk has been defined in a particular situation, then a separate and different determination must be made, i.e., that of the degree of acceptability of the defined risk. This process often involves many value-laden judgments and the interaction of diverse social forces. It commonly comes to resolution, although frequently an unstable and temporary resolution, in the political arena. Lowrance emphasized the importance of factual evidence as essential to reasonable assessment of risk and determination of risk acceptability.

In some circumstances, a determination of risk acceptability might be conditional in the sense of requiring that spore levels at and around a compost site should not exceed some predetermined concentration. Although details are not provided here, moderately quantitative methods of monitoring the air for spores of A. fumigatus are known (144).

Even in the absence of information adequate to support quantitative assessments of risk, measures to avoid, alleviate, or protect against possible hazards associated with A. fumigatus are currently being incorporated into the design criteria for composting sites. In the Washington, D.C., metropolitan area, for example, enclosed structures are planned to house equipment for the screening out of wood chips after composting. Proximity of planned composting operations to health-care facilities is under careful scrutiny. Aerial dispersal patterns of A. fumigatus spores are becoming better understood, air-sampling methods for such spores are being improved, and aerometric monitoring for spores is planned or in progress at several locations. Preemployment health screening of employees applying for work at composting sites is under serious consideration. Thus, in parallel with preventive or protective measures against odor, noise, dust, and other possible hazards or annoyances, so too, measures against A. fumigatus are currently being planned and may be expected to be included as future experience dictates in sludge-composting operations. Acceptability of risk, like the

acceptability of expenditure of public funds, is obviously a matter for informed public judgment. Ultimate decisions on these matters may be expected after public discussion and the operation of the political process through duly authorized public agencies and officials.

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